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NEUROBEHAVIOURAL AND COGNITIVE DEVELOPMENT IN INFANTS BORN TO MOTHERS WITH EATING DISORDERS

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ABSTRACT

Introduction: Although recent research has focused on the effects of maternal eating disorders on children, little is known about the effect of maternal eating disorders on neurobiological outcomes in newborns and infants. The present study is the first to investigate neurobehavioural regulation and cognitive development in newborns and infants of mothers with eating disorders (ED).

Methods: Women with an active and past ED, and healthy controls were recruited to a prospective longitudinal study during their first trimester or second trimester of pregnancy. Newborns and infants of mothers with ED were compared to newborns and infants of healthy controls on: a) neurobehavioural dys-regulation using the Brazelton Neonatal Behavioural Assessment Scale (NBAS) at 8 days post-partum (active ED, n=15; past ED, n=20; healthy controls, n=28); and b) cognitive development using the Bayley Scales of Infant and Toddler Development (BSID-III) at one year post-partum (active ED, n=18; past ED, n=19; healthy controls, n=28). In order to maintain the largest possible sample at each time point, sample size varied across time points.

Results: Newborns of mothers with an active ED had worse autonomic stability when compared to newborns of healthy controls (B=-0.34 (-1.81,-0.26)). Infants of mothers with a past ED had poorer language (B=-0.33(-13.6,-1.9)) and motor development (B=-0.32(-18.4,-1.3)) compared to healthy controls.

Conclusion: Children of mothers with ED display neurobehavioural dys-regulation early after birth, and poorer language and motor development at one year. These characteristics suggest evidence of early neurobiological markers in children at risk. Differential outcomes in children of women with active vs. past ED suggest that active symptomatology during pregnancy might have an effect on physiological reactivity whilst cognitive characteristics might be more stable markers of risk for ED.

Keywords: NBAS, BSID, eating disorders, child development

Abbreviations: Brazelton Neonatal Behavioural Assessment Scale (NBAS), Bayley Scales of Infant and Toddler Development (BSID-III).

INTRODUCTION

Eating Disorders (ED) encompass Anorexia nervosa (AN), Bulimia nervosa (BN) and Binge Eating Disorder (BEN) and affect women of childbearing age(APA, 2013). Intergenerationally, ED in motherhood has been associated with an increased risk of unplanned pregnancies(Easter, Treasure, & Micali, 2011) as well as birth complications(Easter, Taborelli, & Micali, 2010; Micali, Simonoff, & Treasure, 2007). Children of mothers with ED have higher levels of general psychopathology in childhood and early adolescence(Micali, Stahl, Treasure, & Simonoff, 2013a; Micali, Stavola, Ploubidis, Simonoff, & Treasure, 2013b), and difficulties with feeding and eating(Micali, Simonoff, Stahl, & Treasure, 2011; Micali, Simonoff, & Treasure, 2009; Stein & Fairburn, 1989). Offspring of mothers with ED may be at increased risk for adverse developmental outcomes over a number of different domains(Park, Senior, & Stein, 2003; Patel, Wheatcroft, Park, & Stein, 2002).

Research from our group has shown that children born to mothers with ED show specific cognitive profiles both early and later in childhood(Kothari, Rosinska, Treasure, & Micali, 2013a; Kothari, Solmi, Treasure, & Micali, 2013b). Children of mothers with ED have difficulties in social understanding, visual-motor function and aspects of executive functioning(Kothari, Barona, Treasure, & Micali, 2015) as well as general intelligence(Kothari et al., 2013b). It is unclear whether these are: early markers of general 'risk', akin to intermediate phenotypes; the effect of specific 'insults' *in utero*; either metabolic (via maternal poor nutrition and metabolic imbalance) or stress-mediated (via elevated stress during pregnancy)(Micali & Treasure, 2009); or via other mechanisms affecting brain development. Disentangling these effects is complex, as children of mothers who had active ED in pregnancy may show abnormal development due to in utero effects and/or a genetic risk of ED.

Substantial literature indicates that the *in utero* environment can affect both short-term (foetal and infant) and long-term (child-adulthood) development(Barker, 1998). Both neurobehavioural dys-regulation and cognitive development have been studied in mothers with depression and anxiety (Goodman et al., 2011; Laplante, Brunet, Schmitz, Ciampi, & King, 2008). Newborns of depressed and anxious mothers are more likely to show decreased motor tone, more abnormal reflexes, lower

activity levels and increased irritability(Alder, Fink, Bitzer, Hosli, & Holzgreve, 2007). Maternal high stress has been shown to predict developmental motor delays in infants(Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003), lower cognitive and linguistic abilities(Laplante et al., 2008) attention deficit hyperactivity disorder (ADHD) symptoms, externalising behaviours, and anxiety in childhood(Van den Bergh & Marcoen, 2004).

There is a paucity of research investigating the trajectory of the offspring of mothers with ED. Importantly, no studies have examined outcomes of infants of mothers with ED's this young. Furthermore, this will be the first study from this dataset with a focus on child development. Given the importance of the role of newborn and infant development in later child development and health, it is important to be able to identify early risk markers and follow-up children through childhood in order to investigate development.

The aims of this study were to investigate: 1. Whether maternal ED are associated with newborn neurobehavioural dys-regulation at 8 days postpartum and infant development at one year; 2. Whether maternal active vs. past ED would have a differential effect on child outcomes; 3. To explore whether maternal psychopathology (ED, depression, anxiety) and stress physiology in *utero* might explain any abnormalities in newborn neurobehavioural dysregulation and infant development.

METHODS

Design and participants

The Nutrition and Stress in Pregnancy (NEST-p) study is an observational prospective study of mothers and their children. The aim of the NEST-p study was to examine *in utero* mechanisms and pathways related to adverse perinatal and infant outcomes in the offspring of mothers with ED (Easter et al., 2013; Easter et al., 2015).

Women were recruited for this study during the first or second trimester of pregnancy. The initial core NEST-p sample consisted of 137 mothers, of whom 37 had an active ED, 39 had a past ED and 61 were healthy controls. Women were recruited from antenatal care and specialist ED services. For

detailed recruitment methods and study design see Easter et al. (Easter et al., 2013; Easter et al., 2015).

Exposure

Eating disorder diagnosis: ED diagnosis was determined at baseline using the Structured Clinical Interview for Axis I DSM-IV-TR Disorders (SCID-I)(First, Spitzer, Gibbon, & Janet, 2002). The SCID-I is a semi-structured diagnostic interview used to determine Axis I DSM-IV-TR disorders(Association, 2000).

Outcomes

In order to maintain the largest possible sample at each time point (8 days post-partum and one year), we included dyads with complete data at each time point. Therefore, women included at each time point vary slightly.

Eight days postpartum (neurobehavioral function)

Brazelton Neonatal Behavioural Assessment Scale (NBAS)(Brazelton & Nugent, 1995b) was used to assess newborn functioning and performed by two researchers who were trained and certified (F.C. and S.P.) and who were blind to maternal diagnosis. The instrument measures the infant's strengths and difficulties in social emotional development(Als, Tronick, Lester, & Brazelton, 1977). The NBAS consists of 28 behavioural and 28 reflex items. The most commonly used method of data reduction for the NBAS is the Lester cluster scoring method(Lester & Brazelton, 1982), which reduces the data into six behavioural and one reflex cluster: orientation, motor organisation, regulation of state, autonomic organisation, range of state, reflexes and habituation. The NBAS shows high inter-rater and predictive validity (Als et al., 1977). Factor analysis have shown the test discriminates between preterm and term infant behaviour and differentiates small-for-gestational age (SGA) infants and asphyxiated infants from typically developing infants(Brazelton & Nugent, 1995a). Higher scores on behavioural items indicate better performance, whilst higher scores on the reflex cluster indicate deviant reflexes.

Mother-child dyads took part in the newborn assessment during the early neonatal period at mean age 8.73 days postnatal (range: 5 – 30 days).

Mother-child dyads were included in the analyses investigating neurobehaviour of newborns if complete data was available on NBAS and maternal ED (N=64). In this subsample of the study, 15 women were active ED cases, 20 were past ED cases and 28 were healthy controls.

One year (general development)

Bayley Scales of Infant and Toddler Development (BSID-III)(Bayley, 2006) were used to assess neurodevelopment of infants at one year of age. The measure was designed to be administered individually to young children, aged 1 to 42 months; it consists of three scales: cognitive, language (including receptive and expressive communication sub-scales) and motor (including fine and gross motor subtests). The measure was administered by a trained researcher (ET).

Scales and subscales scores are converted into scaled scores (M=10, SD=3) then into normally distributed composite test scores, scaled on a range of 40-160 (M=100, SD=15).

Mother-child dyads were included in the analyses investigating neurodevelopment if complete data was available on BSID-III and maternal ED diagnosis (N=68). In this subsample of the study, 18 women were active ED cases, 19 were past ED cases and 28 were healthy controls.

Maternal psychopathology

ED, depression and anxiety symptoms were assessed during the third trimester of pregnancy using the following measures:

Eating Disorder Examination Questionnaire (EDE-Q)(Fairburn & Beglin, 1994) was used to assess ED symptoms. The EDE-Q is a 28-item self-reported questionnaire focused on ED symptoms and behaviours within the last 28 days. Items are scored using a 7-point, force-choice rating scheme rating

presence and frequency of ED behaviours. A global score can be derived, in addition to four subscales:

Beck Depression Inventory (BDI)(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was used to assess women's symptoms of depression. The BDI is a 21-item multiple choice self-report measure measuring intensity and severity of depression symptoms during the last week. A total score is derived ranging from normal to extreme depression.

Spielberger State-Trait Anxiety Inventory (STAI)(Lushene, Gorsuch, & Spielberger, 1970) was used to assess women's anxiety. This is a 40-item self-reported measure consisting two 20-item scales which distinguish state (e.g. temporary condition in specific situations) and trait (e.g. general tendency to perceive situations as threatening) anxiety.

Socio-demographic data/covariates

Socio-demographic data on maternal age, marital status of mothers (married or cohabitating versus not), maternal education (up to O level/GCSE equivalent versus A level and above) and ethnicity (white versus non-white) were obtained via self-report at recruitment to the main study. Birthweight data were collected at time of birth via obstetric records.

Exploratory variables

Maternal cortisol decline

Maternal salivary cortisol was obtained to explore the effect of biological measures of stress during pregnancy. Saliva samples were measured at three time-points in the day (on awakening, 30 minutes past awakening and at 8pm on the same day), on two consecutive days. During the third trimester participants were provided with six labelled tubes which contained oral swabs for saliva collection. Detailed instructions were given both verbally and written. Once posted, samples were immediately

frozen and stored at -20C. The mean time at which the samples were taken was comparable between the three main exposure groups: active ED group (33 weeks), recovered ED group (33.1 weeks) and healthy control group (33.5 weeks).

For the purpose of this study a measure of cortisol decline was calculated as an indicator of Hypothalamic-Pituitary-Adrenal (HPA) axis functioning during pregnancy. Cortisol decline was calculated by subtracting evening cortisol levels from cortisol levels on awakening. Cortisol decline was chosen as a marker since women with active ED in the present study have previously been found to display lower cortisol declines (reflective of cortisol dysregulation) during pregnancy. For the full collection and analysis protocol see Easter, et al(Easter et al., Under review).

Attrition and Missingness

Missingness on outcome data was investigated. By the time of birth, the sample consisted of 101 women of the initial 137. Overall, 63 women (62.4% of total) participated to the 8 days post-partum assessment and 65 women (64.4% of total) on the BSID. We investigated differences between women with complete data; missingness at each time point was not predicted by ED status, maternal age, education or marital status. Missing data on outcomes were therefore assumed to be at random.

We investigated missingness amongst women with complete data on exposure and outcome at each time point separately. Multiple random imputation was used to deal with missing confounder data and both predictor and outcomes were used in the model. Missing data were imputed for maternal education, ethnicity, marital status and child birthweight. Results for both complete and imputed cases were almost identical, consequently the results based on the imputed cases are presented here as multiple imputation is assumed to correct bias.

Statistical analyses

All variables were examined to check for inconsistencies and outliers and normality using tabulations, graphs and plots.

The distribution of covariates was studied according to the main predictor using chi-square or t-tests depending of the type of variable.

Associations between maternal ED and newborn neurobehaviour and development was investigated using crude and adjusted linear regression analyses. *A priori* confounders (maternal education, age and child gender) were included in all adjusted models. A second set of models was also carried out adjusting for anxiety or depression depending on associations between the main outcome and these variables. Further post hoc analyses were conducted in order to investigate associations between specific maternal ED diagnoses (lifetime AN and lifetime BN) and outcomes under study.

Correlation analyses were run to investigate the correlation between outcomes and maternal psychopathology during the third trimester of pregnancy (EDEQ, BDI and STAI), and maternal stress response in pregnancy (cortisol decline).

All analyses were run using SPSS 23 and a two-tailed significance level of $p \leq 0.05$ was used.

RESULTS

A. Socio-demographic data

Socio demographic characteristics of the sample at birth were studied across women and are shown in Table 1.

B. Newborn behaviour

Newborns of mothers with active ED were more likely to have lower scores in autonomic stability compared to healthy controls (B = -0.37, 95% CI: -1.71/-0.32) (Table 2). These differences persisted after adjusting for relevant confounders (B = -0.34, 95% CI: -1.81/-0.26). Autonomic stability in newborns of mothers with active ED remained different compared to healthy controls (B=-0.42, 95% CI: -2.14/-0.11) after adjusting for trait anxiety. There was weak evidence that motor organisation was worse in offspring of mothers with active ED (B = -0.38, 95% CI: -1.67/0.04). Measures of newborn

behaviour were comparable in the past ED and healthy control group. Furthermore, no differences were found across specific ED diagnoses (AN, BN, BED) and behavioural dys-regulation in exploratory analyses.

C. Infant neurodevelopment

Results are shown in table 3. Infants of mothers with active ED were more likely to have lower scores on the language receptive scale (B = -0.31, 95% CI: -3.2/-0.2) and language composite scale (B = -0.31, 95% CI:-13.4/-1.1) in crude analyses. These associations decreased in strength and became non-significant after adjustment. Differences in scores on the language receptive scale (B= -0.37, 95% CI: -3.6/-0.6), language composite scale (B = -0.36, 95% CI: -14.8/-2.3), fine motor scale (B = -0.39, 95% CI: -3.9/-0.8), gross motor scale (B = -0.34, 95% CI: -4.1/-0.4) and motor composite scale (B= -0.31, 95% CI:-18.1/-1.2) between infants of mothers with past ED and controls remained and were significant after adjusting for relevant confounders (see table 3). Adjusting for trait anxiety in post-hoc analyses, gross motor development still differed in infants of mothers with past ED compared to controls (B= -0.4, 95% CI: -3.9/-0.5).

Exploratory analyses showed that infants of mothers with a lifetime diagnosis of AN (N=20) were more likely to have poorer receptive language (B= -0.3, 95% CI: -2.9/-0.2), overall language (B= -0.2, 95% CI: -12.5/-1.1) and gross motor development (B= -0.2, 95% CI: -3.8/-0.4) compared to infants of healthy control mothers. Infants of mothers with a lifetime diagnosis of BN (N=15) were more likely to have lower overall cognitive development (B= -0.3, 95% CI: -14.0/-1.4), receptive language (B= -0.2, 95% CI: -3.0/-0.0) and motor development (B= -0.2, 95% CI: -17.9/-2.8) compared to infants of healthy control mothers.

D. Correlations between newborn behaviour, child neurodevelopment and maternal psychopathology in pregnancy

Results are shown in table 4. Overall, maternal ED psychopathology and trait anxiety were negatively correlated with autonomic stability and motor organisation. Language and motor development in

infants were found to be negatively correlated with several aspects of maternal ED psychopathology and anxiety, both trait and state.

E. Correlations between maternal cortisol decline, newborn behaviour and infant development

Maternal cortisol decline in pregnancy showed a negative correlation with fine motor development (rho= -0.258, p=0.05), but was not correlated with any newborn neurobehaviour aspect or other aspects of infant cognitive development.

DISCUSSION

The present study shows that maternal ED are an important predictor of newborn neurobehaviour and infant development. In line with our initial hypothesis and previous research, we found that newborns of mothers with an active ED during pregnancy had worse autonomic stability and motor organisation compared to newborns of healthy mothers. In infancy, offspring of ED mothers had poorer language development, (both receptive and overall language), as well as poorer motor development, including gross motor development. Maternal psychopathology in pregnancy (ED, depression and anxiety) was correlated with offspring development, and maternal trait anxiety explained some of the association between maternal ED and newborn/infant outcomes. Exploratory analyses suggested an effect of maternal lifetime AN on offspring receptive and composite language. In line with our hypotheses maternal HPA axis dysfunction was correlated with offspring development (motor fine development).

No previous research has investigated neurobehavioral responses in children of mothers with ED. In our study, maternal active ED predicted worse autonomic stability (e.g. more tremulousness and startles), meaning that newborns of mothers with an active ED had more difficulties regulating their breathing, temperature and the rest of the autonomic system. Although each system (orientation, motor, regulation and autonomic) can be observed independently, they all interact with each other. The autonomic system forms the basis on which all other systems develop and therefore dys-regulation in this system could compromise all other systems (e.g. on the basis of physiological

stability, motoric control becomes possible). Although there is limited research on the effect of autonomic dysregulation later in life, a study by Russel and colleagues found that autonomic instability in newborns was correlated with infant temperament (i.e. fussiness and unpredictability)(Isabella, Ward, & Belsky, 1985). Previous research has found that mothers with ED report their children as having a more difficult temperament in infancy(Barona, Nybo Andersen, & Micali, 2016) and increased stress response (Als, 1977). Autonomic dysregulation at six days post-partum might therefore be an early marker of temperamental problems or stress response.

Research has shown that newborns of mothers who are exposed to high levels of maternal depression, anxiety and stress during pregnancy show autonomic instability(Field et al., 2003). In our sample, autonomic instability was correlated with overall ED psychopathology and trait anxiety however, the association between maternal active ED and autonomic instability persisted after adjusting for trait anxiety, thus suggesting a possible specific effect of maternal eating disorder psychopathology. These findings and our findings of an association with maternal active ED only, might index a role for *in utero* factors in explaining newborn autonomic instability. Importantly, as the assessment is conducted at eight days post-partum, there is limited postnatal/environmental effects, which strengthens the hypothesis of *in utero* factors. For example nutrition, stress and smoking might play a role. The period in gestation between 24 and 42 weeks is particularly vulnerable to nutritional insults because of the rapid trajectory of several neurological processes such as synapse formation and myelination(Fuglestad, Rao, Georgieff, & Code, 2008). Another possible hypothesis is the effect of smoking during pregnancy as nicotine can transfer across the placenta and interfere with brain development (Kinney, O'Donnell, Kriger, & White, 1993).

It is important to note that although autonomic instability was only associated with active ED, newborns of mothers with a past ED also had lower autonomic stability, trending for statistical significance. Therefore autonomic stability might be an early biomarker of the effects of maternal ED on the offspring or an intermediate phenotype of ED. However, further longitudinal research is needed to clarify this.

Results on maternal ED and their effect on offspring development(Micali et al., 2013a; Micali et al., 2013b) are consistent with our previous work and in line with previous research highlighting the role of maternal psychopathology in the perinatal period and its impact on early child development. Infants of mothers with a lifetime ED diagnosis had lower scores in language development, both receptive and composite scores and motor composite and gross motor scores. These results are in line with our previous findings on cognitive development in children of mothers with ED at age three and a half(Kothari et al., 2013a). The associations between maternal ED and language development were similar across active and past ED, whilst motor development was more affected in offspring of women with past ED. These results point to an effect of maternal ED psychopathology over time or postnatally, rather than specific *in utero* mechanisms.

Although higher maternal anxiety scores during pregnancy were correlated with poorer language and motor development, after adjusting for this in our regression analyses, the association between gross motor development and maternal past ED continued to be significant, whilst language scores became non-significant. One possible explanation for these findings is that, consistent with the initial hypothesis, anxiety might be the main driver for the association identified between maternal ED and infant cognitive development. Lower motor stability at birth in this study corroborates this evidence. A study by Feldman and Eidelman found that motor scores in the NBAS predicted motor development in the BSID at 24 months(Feldman & Eidelman, 2006). These results are consistent with prior findings from our group that children of mothers with ED had poor performance in the locomotor domain at 18 months(Kothari et al., 2013a). Motor development and functioning has not received much attention in the ED field. However, previous research in areas of language development has shown that early motor development, such as gesture and pointing, are tightly related to development of speech in the first years in both children who are typically developing and those with an atypical development. Interestingly, this has been studied in children at high-familial risk for autism suggesting that the early gesture delays in this group could be attributed to a later language delay more generally(LeBarton & Iverson, 2016). In this study, we found a clear pattern of

motor deficits as well as language ones. Although this needs further investigation, it corroborates earlier research studying the correlation between motor and language development.

Whilst it was maternal active ED that predicted worse scores in newborn neurobehaviour, it was maternal past ED that predicted worse scores in infant development at one year. Both groups, active and past ED were similar in sample size and demographics, and only differed on maternal age. It is important to note, that since cognitive development was studied at one year, postnatal environment might influence results. However, one possible hypothesis for our results, is that physiologic reactivity is more susceptible to 'state' in terms of maternal ED (given its association with maternal pregnancy ED only); whilst cognitive characteristics might be markers of risk for ED, e.g. intermediate or endophenotypes (Micali & Dahlgren, 2016) or broader markers of susceptibility to general psychopathology (given their correlation with maternal anxiety and depression measures) (Skovgaard et al., 2008) . Existing research suggests that individuals with ED show differences in cognitive profiles when compared to healthy controls, which could contribute to either onset or maintenance of the disorder. Further longitudinal research is needed in order to determine if poorer language and motor development index predisposition for ED or general psychopathology.

Strengths and Limitations

This study has several strengths; firstly, it is the first study to investigate early child development (newborn neurobeheaviour and cognition) in a sample of women with an active and past ED. Very few studies have followed women with ED from pregnancy onwards longitudinally. Moreover, this study has a further strength in the use of detailed objective offspring assessments, rather than questionnaires. We studied ED transdiagnostically, but also explored differences in child outcomes according to maternal ED diagnosis.

We included women who were not seeking treatment or referred for treatment, therefore making our study more generalizable.

The main limitation of this study, however, is the sample size and attrition. As often occurs in longitudinal studies, women were lost to follow up from initial recruitment, thus leading to relatively

small sample sizes, and low power to detect potential differences. Furthermore, because of the sample size we were only able to run exploratory analyses to investigate the effects of maternal ED diagnoses. However, given that this is the first study of its kind our study provides initial evidence that can be further assessed in larger samples.

Conclusions

Children of mothers with ED have poorer autonomic regulation in the early postnatal phase and language and motor developmental difficulties at one year. These results highlight early markers of susceptibility for adverse temperament or stress reactivity (autonomic instability), and neurocognitive characteristics that might be ED intermediate phenotypes. Identifying early developmental patterns and features in children at risk for ED might help us understand the pathophysiology of ED and highlight early signs of vulnerability.

Key points

- Children of mothers with active ED display neurobehavioural dysregulation early after birth.
- Children of mothers with past ED display poorer language and motor development at one year.
- Differences in outcomes in children of women with active vs. past ED suggest an effect of active ED symptomatology during pregnancy on newborns physiological reactivity whilst outcomes at 1 year could also represent a more stable makers for risk for ED.

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ETHICAL CONSIDERATIONS

Written consent was obtained from the subjects.

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REFERENCES

Alder, J., Fink, N., Bitzer, J., Hosli, I., & Holzgreve, W. (2007). Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. *J Matern Fetal Neonatal Med, 20*(3), 189-209. doi: 10.1080/14767050701209560

Als, H., Tronick, E., Lester, B. M., & Brazelton, T. B. (1977). The Brazelton neonatal behavioral assessment scale (BNBAS). *Journal of abnormal child psychology, 5*(3), 215-229.

APA. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*: American Psychiatric Pub.

Association, A. P. (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association.

Barker, D. J. P. (1998). *Mothers, babies and health in later life*. London: Churchill Livingstone.

Barona, M., Nybo Andersen, A. M., & Micali, N. (2016). Childhood psychopathology in children of women with eating disorders. *Acta Psychiatrica Scandinavica*, 295-304. doi: 10.1111/acps.12616

Bayley, N. (2006). *Bayley scales of infant and toddler development, third edition*. San Antonio, TZ: Harcourt Assessment, Inc.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry, 4*, 561-571.

Brazelton, T. B., & Nugent, J. K. (1995a). *Neonatal Behavioral Assessment Scale* (3rd Edition ed.). Clinics in Developmental Medicine No. 137: London: Mac Keith Press.

Brazelton, T. B., & Nugent, J. K. (1995b). *Neonatal behavioral assessment scale*: Cambridge University Press.

Easter, A., Bye, A., Taborelli, E., Corfield, F., Schmidt, U., Treasure, J., & Micali, N. (2013). Recognising the symptoms: how common are eating disorders in pregnancy? *European eating disorders review : the journal of the Eating Disorders Association, 21*(4), 340-344. doi: 10.1002/erv.2229

Easter, A., Solmi, F., Bye, A., Taborelli, E., Corfield, F., Schmidt, U., . . . Micali, N. (2015). Antenatal and postnatal psychopathology among women with current and past eating disorders:

longitudinal patterns. *European eating disorders review : the journal of the Eating Disorders Association, 23*(1), 19-27. doi: 10.1002/erv.2328

Easter, A., Taborelli, E., Bye, A., Zunszain, P., Pariante, C., Treasure, J., . . . Micali, N. (Under review). Perinatal hypothalamic-pituitary-adrenal axis regulation among women with eating disorders and their infants.

Easter, A., Taborelli, E., & Micali, N. (2010). Obstetric outcomes amongst women with a history of anorexia nervosa. *Minerva Psichiatrica, 51*(3), 161-175.

Easter, A., Treasure, J., & Micali, N. (2011). Fertility and prenatal attitudes towards pregnancy in women with eating disorders: results from the Avon Longitudinal Study of Parents and Children. *Bjog, 118*(12), 1491-1498. doi: 10.1111/j.1471-0528.2011.03077.x

Fairburn, C. G., & Beglin, S. J. (1994). Assessment of eating disorders: interview or self-report questionnaire? *Int J Eat Disord, 16*(4), 363-370.

Feldman, R., & Eidelman, A. I. (2006). Neonatal state organization, neuromaturation, mother-infant interaction, and cognitive development in small-for-gestational-age premature infants. *Pediatrics, 118*(3), e869-878. doi: 10.1542/peds.2005-2040

Field, T., Diego, M., Hernandez-Reif, M., Schanberg, S., Kuhn, C., Yando, R., & Bendell, D. (2003). Pregnancy anxiety and comorbid depression and anger: Effects on the fetus and neonate. *Depression and Anxiety, 17*(3), 140-151. doi: 10.1002/da.10071

First, M., Spitzer, R., Gibbon, M., & Janet, B. (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP)*. New York State Psychiatric Institute: New York: Biometrics Research.

Fuglestad, A. J., Rao, R., Georgieff, M. K., & Code, M. M. (2008). The role of nutrition in cognitive development. *Handbook in Developmental Cognitive Neuroscience, 2*, 623-641.

Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M., & Heyward, D. (2011). Maternal depression and child psychopathology: a meta-analytic review. *Clinical Child and Family Psychology Review, 14*(1), 1-27.

Huizink, A. C., Robles de Medina, P. G., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. (2003). Stress during pregnancy is associated with developmental outcome in infancy. *Journal of child psychology and psychiatry, and allied disciplines, 44*(6), 810-818.

Isabella, R. A., Ward, M. J., & Belsky, J. (1985). Convergence of multiple sources of information on infant individuality: Neonatal behavior, infant behavior, and temperament reports. *Infant Behavior and Development, 8*(3), 283-291.

Kinney, H. C., O'Donnell, T. J., Kriger, P., & White, W. F. (1993). Early developmental changes in [3H]nicotine binding in the human brainstem. *Neuroscience, 55*(4), 1127-1138.

Kothari, R., Barona, M., Treasure, J., & Micali, N. (2015). Social cognition in children at familial high-risk of developing an eating disorder. *Front Behav Neurosci, 9*, 208. doi: 10.3389/fnbeh.2015.00208

Kothari, R., Rosinska, M., Treasure, J., & Micali, N. (2013a). The Early Cognitive Development of Children at High Risk of Developing an Eating Disorder. *European Eating Disorders Review*.

Kothari, R., Solmi, F., Treasure, J., & Micali, N. (2013b). The neuropsychological profile of children at high risk of developing an eating disorder. *Psychological medicine, 43*(7), 1543-1554. doi: 10.1017/S0033291712002188

Laplante, D. P., Brunet, A., Schmitz, N., Ciampi, A., & King, S. (2008). Project Ice Storm: prenatal maternal stress affects cognitive and linguistic functioning in 5 1/2-year-old children. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(9), 1063-1072. doi: 10.1097/CHI.0b013e31817eec80

LeBarton, E. S., & Iverson, J. M. (2016). Gesture development in toddlers with an older sibling with autism. *International Journal of Language & Communication Disorders, 51*(1), 18-30. doi: 10.1111/1460-6984.12180

Lester, B. M., & Brazelton, T. B. (1982). Cross-cultural assessment of neonatal behavior. In D. Waquer & H. Stepherson (Eds.), *Cultural perspectives in child development* (pp. 20-53). San Francisco: W.H. Freeman.

Lushene, R., Gorsuch, R., & Spielberger, C. (1970). Manual for the state-trait anxiety inventory.

Micali, N., & Dahlgren, C. L. (2016). All that glisters is not an endophenotype: rethinking endophenotypes in anorexia nervosa. *European child & adolescent psychiatry, 25*(11), 1149-1150. doi: 10.1007/s00787-016-0910-x

Micali, N., Simonoff, E., Stahl, D., & Treasure, J. (2011). Maternal eating disorders and infant feeding difficulties: maternal and child mediators in a longitudinal general population study. *Journal of child psychology and psychiatry, and allied disciplines, 52*(7), 800-807. doi: 10.1111/j.1469-7610.2010.02341.x

Micali, N., Simonoff, E., & Treasure, J. (2007). Risk of major adverse perinatal outcomes in women with eating disorders. *The British Journal of Psychiatry, 190*(3), 255-259.

Micali, N., Simonoff, E., & Treasure, J. (2009). Infant feeding and weight in the first year of life in babies of women with eating disorders. *The Journal of pediatrics, 154*(1), 55-60. e51.

Micali, N., Stahl, D., Treasure, J., & Simonoff, E. (2013a). Childhood psychopathology in children of women with eating disorders: understanding risk mechanisms. *Journal of child psychology and psychiatry, and allied disciplines*. doi: 10.1111/jcpp.12112

Micali, N., Stavola, B., Ploubidis, G. B., Simonoff, E., & Treasure, J. (2013b). The effects of maternal eating disorders on offspring childhood and early adolescent psychiatric disorders. *International Journal of Eating Disorders*.

Micali, N., & Treasure, J. (2009). Biological effects of a maternal ED on pregnancy and foetal development: a review. *European eating disorders review : the journal of the Eating Disorders Association, 17*(6), 448-454. doi: 10.1002/erv.963

Park, R. J., Senior, R., & Stein, A. (2003). The offspring of mothers with eating disorders. *European child & adolescent psychiatry, 12*(1), i110-i119.

Patel, P., Wheatcroft, R., Park, R. J., & Stein, A. (2002). The children of mothers with eating disorders. *Clinical Child and Family Psychology Review, 5*(1), 1-19.

Skovgaard, A. M., Olsen, E. M., Christiansen, E., Houmann, T., Landorph, S. L., & Jorgensen, T. (2008). Predictors (0-10 months) of psychopathology at age 11/2 years - a general population study in The Copenhagen Child Cohort CCC 2000. *Journal of child psychology and psychiatry, and allied disciplines, 49*(5), 553-562. doi: 10.1111/j.1469-7610.2007.01860.x

Stein, A., & Fairburn, C. G. (1989). Children of mothers with bulimia nervosa. *BMJ: British Medical Journal, 299*(6702), 777.

Van den Bergh, B. R., & Marcoen, A. (2004). High Antenatal Maternal Anxiety Is Related to ADHD Symptoms, Externalizing Problems, and Anxiety in 8-and 9-Year-Olds. *Child development, 75*(4), 1085-1097.

Table 1. Socio-demographic characteristics

	Active **N= 18**	**Past** **N= 19**	**Unexposed** **N= 28**	**Statistic, p-value**
Ethnicity %				
White	13 (72.22%)	16 (84.21%)	24 (85.71%)	χ2= 1.45, p=0.48
Other ethnic background	5 (27.77%)	3 (15.79%)	4 (14.29%)	
Marital status %				
Single not cohabitating	3 (16.67%)	3 (15.79%)	2 (7.14%)	χ2= 2.52, p=0.28
Married/cohabitating	15 (83.33%)	16 (84.21%)	26 (92.86%)	
Education %				
No formal education/GCSEs	2 (11.11%)	1 (5.26%)	1(3.57%)	χ2= 0.94, p=0.63
A levels/higher	16 (88.89%)	12 (63.16%)	26 (92.86%)	
Maternal age, mean (SD)	30.17 (5.74)	34.47 (3.96)	34.00 (3.34)	F= 5.78, p=0.01***
Birthweight (gr), mean (SD)	3129.26 (601.58)	3485.41 (411.28)	3384.83 (412.64)	F= 3.56, p=0.04*

*p≤0.05, **p≤0.01, ***p≤0.001, †p<0.1

**Socio-demographics were studied in the largest sample, no significant differences were found between samples at 8 days post-natal and 1 year.

Table 2. Associations between newborn behaviour and maternal ED: mean scores, crude and adjusted regression coefficients from linear regression

	Crude (B, 95% CI)		Adjusted (B, 95% CI)[1]		
	Active ED	**Past ED**	**Active ED**	**Past ED**	**HC**
	N=15	N=20	N=15	N=20	N=28
Orientation	-0.21 (-1.2/0.79)	-0.30 (-1.21/0.61)	0.12 (-1.24/2.22)	-0.03 (-1.56/1.33)	Ref
Motor	-0.47 (-1.02/0.09)†	-0.16 (-0.67/0.35)	-0.38 (-1.67/0.04)†	-0.04 (-0.75/0.64)	Ref
Regulation	-0.21 (-0.99/0.57)	-0.21 (-0.93/0.50)	0.19 (-0.68/1.78)	0.06 (-0.87/1.18)	Ref
Autonomic	**-0.37 (-1.71/-0.32)****	-0.24 (-1.23/0.04) †	**-0.34 (-1.81/-0.26)****	-0.24 (-1.43/0.10)†	Ref

*p≤0.05, **p≤0.01, ***p≤0.001, †p<0.1; [1]After adjusting for sex and birth-weight of the baby, maternal age and education.

Table 3. Associations between child development and maternal ED: mean scores, crude and adjusted regression coefficients from linear regression

	Crude (B, 95% CI)[1]		Adjusted (B, 95% CI)[2]		HC
	Active ED	Past-ED	Active ED	Past-ED	
	N=18	N=19	N=18	N=19	N=28
Cognitive Score	-0.27(-11.8/0.2)	-0.13(-8.8/3.3)	-0.23 (-11.1/1.4)	-0.11(-8.4/3.4)	Ref
Language Composite	**-0.31(-13.4/-1.1)***	**-0.36(-14.8/-2.3)****	-0.18(-10.4/2.0)	**-0.33(-13.6/-1.9)****	Ref
Language Receptive	**-0.31(-3.2/-0.2)***	**-0.37(-3.6/-0.6)****	-0.17(-2.4/0.5)	**-0.33(-3.2/-0.5)****	Ref
Language Expressive	-0.20(-1.7/0.3)	-0.23(-1.8/0.2)	-0.13(-1.6/0.6)	-0.21(-1.8/0.2)	Ref
Motor Composite Score	-0.17(-13.5/3.1)	**-0.31(-18.1/-1.2)***	-0.18(-14.4/3.8)	**-0.32(-18.4/-1.3)***	Ref
Fine Motor Scale	-0.12(-2.2/0.9)	-0.18 (-2.6/0.6)	0.07(-2.2/1.3)	-0.17(-2.6/0.7)	Ref
Gross Motor Scale	-0.04(-1.8/-1.4)	**-0.39(-3.9/-0.8)****	-0.04(-1.9/1.4)	**-0.41(-4.1/-0.9)****	Ref

[1]Adjusted for maternal education; [2]Adjusted for child sex and birth-weight of the infant, maternal education and age.

Table 4. Spearman's correlations between maternal psychopathology during pregnancy, child behaviour and development scores

	EDEQ – Total	EDEQ – Restricting	EDEQ – Eating Concern	EDEQ – Weight Concern	EDEQ – Shape Concern	BDI	STAI-S	STAI-T
NBAS								
Orientation	-0.07	-0.08	-0.10	-0.08	-0.00	0.00	-0.02	0.01
Motor	-0.25†	**-0.31***	-0.16	-0.22	-0.23†	-0.24	-0.26	**-0.35****
Regulation	0.00	0.01	-0.08	-0.10	0.10	0.04	0.05	0.08
Autonomic	**-0.27***	-0.24†	-0.25†	-0.25†	-0.25†	-0.26	-0.25	**-0.41****
BSID								
Cognitive Score	-0.20	-0.15	-0.23	-0.25†	-0.25†	-0.24	-0.17	-0.25
Language Receptive	**-0.29***	-0.27†	**-0.37****	**-0.30**	**-0.32***	-0.18	**-0.34***	**-0.29***
Language Expressive	**-0.28***	**-0.37****	**-0.32***	-0.18	-0.25†	0.02	-0.14	-0.09
Language Composite	-0.27†	**-0.30***	**-0.37****	-0.26†	**-0.30***	-0.14	**-0.30***	-0.26
Fine Motor	-0.15	0.01	-0.12	**-0.29***	**-0.28***	-0.17	-0.26	**-0.29***
Gross Motor	-0.26†	-0.27†	-0.24†	-0.27†	-0.24†	-0.25	**-0.41****	**-0.36****
Motor Composite	-0.23	-0.18	-0.27†	**-0.33***	-0.26†	**-0.29***	**-0.42****	**-0.40****

*p≤0.05, **p≤0.01, ***p≤0.001, †p<0.1